



Original Article

The effect of APRV-LTV mechanical ventilation mode on SpO2 and ventilation indices in patients with COVID-19

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ABSTRACT

Background & Aim: Mechanical ventilation is a life-saving method for acute respiratory distress syndrome. The present study aimed to investigate the impact of airway pressure release ventilation-low tidal volume mode on COVID-19 patients' peripheral capillary oxygen saturation and ventilation indices.

Methods & Materials: This clinical trial was conducted on 70 COVID-19 patients hospitalized in the Intensive care unit in Qom, Iran. Patients were selected using convenience sampling and randomly allocated to intervention and control groups. In the control group, patients were ventilated using synchronized intermittent mandatory ventilation mode, and in the intervention group, patients were ventilated using airway pressure release ventilation-low tidal volume mode. Patients' peripheral capillary oxygen saturation and ventilation indices were checked and recorded before and after the intervention. The data were analyzed using SPSS 11.5.

Results: According to the results of the repeated-measures ANOVA test before the intervention and the 2 and 4 hours after the intervention, there were no significant differences between the intervention and control groups regarding the fraction of inspired oxygen, volume minute per minute, and peripheral capillary oxygen saturation ($P>0.05$). However, in the intervention group compared to the control group, the mean of PIP was significantly reduced ($P<0.05$).

Conclusion: In patients with COVID-19, the two modes of mechanical ventilation, APRV, and control, had no significant differences in the fraction of inspired oxygen, volume minute per minute, and peripheral capillary oxygen saturation. However, the mean peak inspiratory pressure reduction in the intervention group was greater than that in the control group. Considering that several factors can affect peripheral capillary oxygen saturation and ventilation indices, these results should be considered with caution.

Introduction

Invasive mechanical ventilation is a life-saving intervention for patients with respiratory failure due to acute respiratory distress syndrome (ARDS), although it may induce ventilator-induced lung injury (1). Therefore, it is necessary to manage patients under mechanical ventilation to prevent and reduce complications related to it. One of the

most important care programs for these patients is monitoring peak inspiratory pressure (PIP). PIP is described as the highest level of pressure applied to the lungs during inhalation. Nurses should keep PIP below 35 to 40 cmH2O. Other parameters that nurses should monitor continuously include volume minute (VM), a fraction of inspired oxygen



(FIO₂), and peripheral capillary oxygen saturation (SpO₂) (2). VM is the volume of gas inhaled or exhaled from a person's lungs per minute; FiO₂ is defined as the amount of oxygen that the ventilator delivers to the patient's lungs; and SpO₂ is the fraction of oxygen-saturated hemoglobin relative to total hemoglobin in the blood (3). Nurses should ensure that the patient is receiving adequate VM with minimal PIP. They also should continuously monitor the SpO₂ and adjust the ventilator settings in such a way as to ensure that the patient has received enough oxygen with the minimum delivery of FIO₂ to patients' lungs. For this purpose, nurses use different modes of mechanical ventilation (4).

Synchronized intermittent mandatory ventilation (SIMV) is a conventional type of volume control mode of ventilation. In this mode, the ventilator provides a mandatory number of breaths at a set volume while allowing spontaneous breathing (5). High PIP and barotrauma are important complications of SIMV mode (6). Also, an airway pressure release ventilation (APRV) mode refers to a limited pressure ventilation mode, which is proven effective in improving patients' oxygenation (7). APRV mode is regarded as a constant positive airway pressure along with alternative declined pressure stages. Besides, low-pressure and high-pressure levels are defined for this ventilation mode. High pressure is set to be longer than low pressure, so there should be enough time to exchange blood gases (8). Some resources define APRV mode as an alternative for volume control ventilation with low tidal volume. Consequently, the patients' exhale phase time would be lowered in this mode, and the inhale phase would take longer (9). Some studies revealed that, compared to other traditional ventilation modes, APRV mode would lead to better oxygenation with minimal complications in the field of increased airway pressure (10). Although peak end-expiratory pressure (PEEP) optimization can help

improve patients' oxygenation, the resulting PIP can lead to lung damage associated with mechanical ventilation (11).

Ventilation using APRV with low tidal volume (APRV-LTV) has been recommended for ARDS patients as well as patients without ARDS symptoms by a great number of clinical experts (12). Implementation of volume control ventilation based on a low tidal volume ratio of 6 ml/kg to the body's ideal weight, a plateau pressure under 30 cmH₂O to a low tidal volume ratio of 12 ml/kg to the body's ideal weight, and a plateau pressure under 50 cmH₂O are associated with a decline in ARDS patients' mortality rate (13, 14). The results of some studies showed that APRV can lead to a better improvement in patient's oxygenation with lower PIP compared to conventional ventilation (15, 16). Some other studies also found that APRV can improve the patient's hemodynamic status and comfort and reduce the need to use sedatives (17, 18).

As mentioned, the results of various studies have shown the benefits of APRV-LTV mechanical ventilation mode in ARDS patients. However, there is a lack of evidence-based knowledge about the usefulness of this mod in COVID-19 patients. Therefore, the present study aimed to investigate the impact of APRV-LTV mode on COVID-19 patients' SpO₂ and ventilation indices.

Methods

Study design

This randomized controlled trial was conducted from September 11, 2021, to November 30, 2021.

Participants

The study population included COVID-19 patients admitted to the Intensive Care Unit (ICU) of Shahid Beheshti Hospital in Qom, Iran. The inclusion criteria were: 1. age above 18 years; 2. no history of chronic respiratory diseases such as chronic

obstructive pulmonary disease (COPD); 3. no history of heavy smoking or alcohol consumption; and 4. completion of the informed consent form by the patient's attorneys. Patients who have been intubated for more than 24 hours, patients whose attorneys did not wish to continue participating in the study, patients who would not tolerate the APRV-LTV mode (arterial blood oxygen saturation would drop by more than 10%) or experienced any new dysrhythmia, and patients who died before the third day of intervention were excluded from the study.

Interventions

After obtaining the authorities' ethical approval and permission, the researchers attended the ICUs of Beheshti Hospital, Qom, Iran, every day. They randomly allocated the COVID-19 patients who met the inclusion criteria and had signed the informed consent form to the intervention and control groups. Patients in the control group were ventilated using SIMV mode during the entire three days of the intervention. In the intervention group, during the three days of the intervention, patients were ventilated from 8 a.m. to 12 p.m. using APRV-LTV mode and from 12 p.m. to 7 a.m. using SIMV mode. Patients' SpO₂ and ventilation indices were checked and recorded at 7:45, 14:00, and 16:00 every day. The settings of APRV-LTV and S-SIMV modes were applied according to the protocols introduced by Hirshberg et al. (9).

Instruments

These patients received mechanical ventilation using the HAMILTON-C2 (Hamilton Medical AG Via Crucis 8, 7402 Bonaduz, Switzerland) device. The data collection sheet consisted of two parts. The first part included demographic (age, gender, and Medical history), and the second part included SpO₂ and ventilation indices (PIP, VM, FiO₂, and). The data collection sheet was

developed based on relevant literature, and experts examined its content and face validity. Sampling and setting of the mechanical ventilation were done by a medical team, including an anesthesiologist, a pulmonologist, and two nurses. The primary outcomes were ventilation indices, and the secondary outcome was SpO₂. A single researcher performed all measurements and data recordings. The devices for measuring SpO₂ and ventilation indices were similar in all patients. In all patients, SpO₂ and ventilation indices were measured noninvasively using vital signs monitoring system with the brand name Sa'a: dat, made in Tehran, Iran, and the monitoring system of mechanical ventilation, respectively.

Sample size

The sample size was calculated using G-Power software. In G-Power, "t-tests" were selected with "Means: Difference between two independent means". The results of Hirshberg et al. showed that the mean airway pressure in the SIMV group and APRV-LTV group were 15±3 and 20±8, respectively (9). Based on the results of Hirshberg et al. and given a type I error probability of 0.05 and a power of 0.80, the sample size was determined to be 35 patients in each group. Participants were initially recruited by the convenience sampling method. Then each individual was randomly allocated to either the intervention or control group.

Randomization

The block randomization method was used to randomly allocate the participants in the study groups utilizing the following website:
<https://www.sealedenvelope.com/simple-randomiser/v1/lists>.

On this website, the sample size of 100 was selected due to the probable attritions. Also, two groups, A and B (A: intervention

group and B: control group), and 4 blocks were selected. The output consisted of 25 blocks. Each block consisted of two “A” and two “B”, which were randomly selected. Selection bias was prevented during the randomization process through the use of a "sealed envelope". Each block was placed in a sealed envelope. The envelopes were numbered in order. The envelopes were opened in order of numbers, and sampling was done based on that block. Sampling continued until the sample size reached 35 in each group.

Data analysis

Study data were analyzed using the Statistical Package for Social Sciences (SPSS, v. 11.5). Before analyzing the findings, the mean of SpO2 and ventilation indices were calculated for each participant in the three days of the intervention in three time periods immediately before, an 2 and 4 hours after the intervention. Then, data analysis was done on these data. RMANOVA, independent t-test, paired t-test, and Chi-square tests were used to compare the quantitative and qualitative variables. The level of significance was set at below 0.05.

Ethical considerations

This research was approved by the ethical committee of Qom Medical Science

University in July 2021 (no. IR.MUQ.REC.1400.065). Moreover, the present study was registered in the Iranian Registry of Clinical Trials database (no. IRCT20150724023314N4). Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975. Through individual interviews, the patients’ attorneys were informed of the study objectives, procedure, and random assignment to the control and intervention groups. They were also informed of the confidentiality of the data. Then, they were asked to review and sign the written informed consent form.

Results

Among 228 COVID-19 patients under mechanical ventilation in the ICU, 118 patients were ineligible to participate in the present study, and 21 were reluctant to participate. The remaining patients were randomly assigned to the two groups of intervention (46 patients) and control (43 patients). According to the exclusion criteria, 11 and 8 patients were excluded from the intervention and control groups, respectively. Finally, 70 patients (35 patients in each group) remained in the study, and their data were analyzed (Diagram 1).

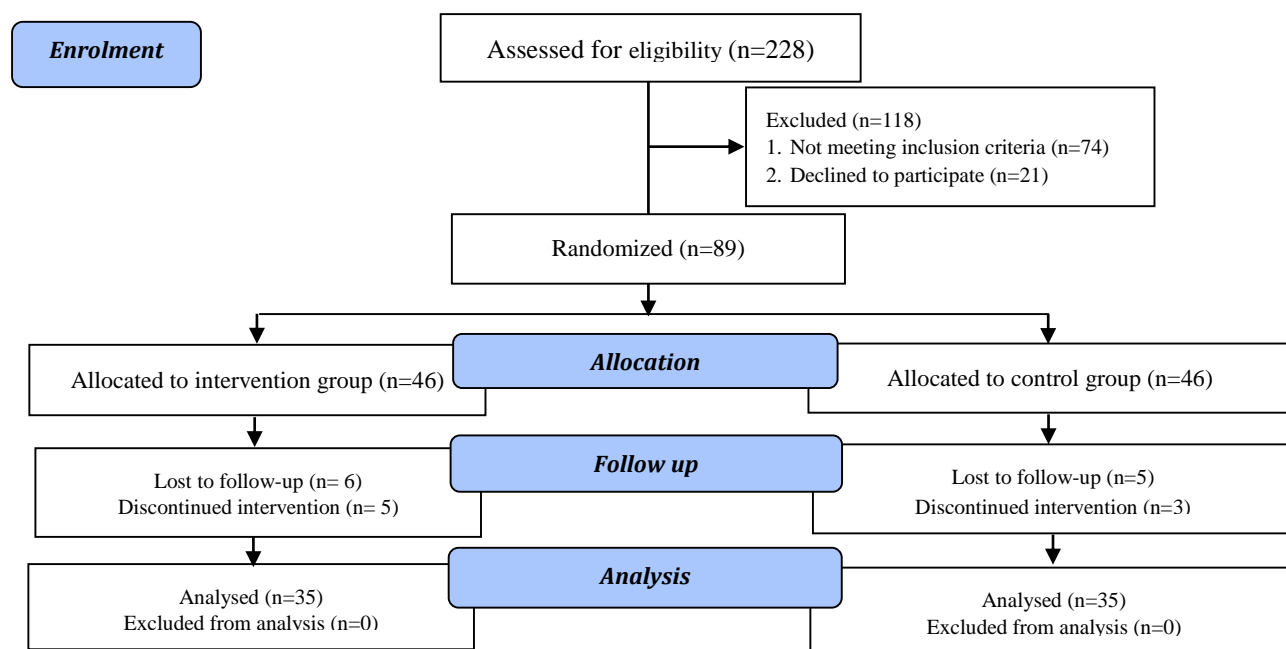


Diagram 1. CONSORT flow diagram

The demographic characteristics of the patients are shown in Table 1. The mean and standard deviation of participants' age in the experimental and the control groups were 55.12 ± 5.89 and 58.02 ± 6.28 years, respectively. Most of the participants were

male (55.7%). Most of the participants (50%) had a history of more than one disease. The independent t-test and Chi-square test results indicate no significant difference between the two groups in terms of age, gender, and medical history ($P > 0.05$).

Table 1. Demographic and clinical characteristics of participants

Variables	Groups		P-value	
	APRV	V-SIMV		
	Mean \pm SD or N (%)	Mean \pm SD or N (%)		
Age	55.12 ± 5.89	58.02 ± 6.28	0.450*	
Gender	Male	18 (51.4)	21 (60)	0.631**
	Female	17 (48.6)	14 (40)	
Medical history	No comorbidity disease	6 (17)	6 (17)	0.856**
	Myocardial infarction	5 (14)	6 (17)	
	Diabetes	7 (20)	5 (14)	
	More than one disease	17 (49)	18 (52)	

* Independent t-test ** Chi-square test

According to the results of the RMANOVA, PIP was the only variable that the two ventilation modes made a difference between the two groups ($P < 0.05$); While regarding VM, FIO₂, and SPO₂, this test did not show any significant difference between the two groups ($P > 0.05$). While the results of RMANOVA also showed that there were no significant group-by-time interaction effects regarding PIP, FIO₂, and SPO₂ ($P > 0.05$,

Table 2, Figure 1-4), there were significant between the group and time interaction regarding the VM ($P < 0.05$). Considering that, T-test with Bonferroni correction was used to compare the effect of two modes on VM at different times. This test showed no statistically significant difference between the two groups regarding VM at any of the measurement times ($P < 0.05$, Table 3).

Table 2. Comparison of the patients' SpO₂ and ventilation indices between APRV-LTV and SIMV groups in the stages of before up to 2 and 4 hours after intervention

Variables	Groups		RMANOVA			
	APRV	SIMV	Within group	Between groups	Tim*Group	
	(Mean \pm SD)	(Mean \pm SD)	P	P	P	
PIP	Before	27.46 ± 6.28	20.96 ± 3.38			
	2 hr After	26.80 ± 5.12	20.96 ± 3.43	.394	.000	.496
	4 hr After	26.67 ± 5.36	20.86 ± 3.96			
VM	Before	10.24 ± 2.24	9.81 ± 1.76			
	2 hr After	9.20 ± 1.97	9.78 ± 1.63	.004	.795	.013
	4 hr After	9.43 ± 1.78	9.68 ± 1.62			
FIO ₂	Before	79.13 ± 22.34	82.84 ± 17.32			
	2 hr After	78.90 ± 22.85	82.66 ± 17.11	.591	.502	.589
	4 hr After	79.17 ± 22.89	82.54 ± 17.39			
SPO ₂	Before	86.30 ± 10.91	88.47 ± 6.73			
	2 hr After	86.10 ± 11.72	87.65 ± 7.21	.272	.441	.352
	4 hr After	85.59 ± 12.42	88.16 ± 6.89			

Abbreviations: SpO₂, peripheral capillary oxygen saturation; FiO₂, fraction of inspired oxygen; PIP, peak inspiratory pressure; VM, volume minute per minute; RMANOVA, Repeated Measures ANOVA

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Table 3. Comparison of the differences of mean SpO2 and ventilation indices before and 2 and 4 hours after intervention in the APRV and SIMV groups

Variables	Stages of intervention	Groups		Independent t-test
		APRV (Mean ± SD)	SIMV (Mean ± SD)	P value
VM	Before	10.24 ± 2.24	9.81 ± 1.76	.422
	2 Hours After	9.20 ± 1.97	9.78 ± 1.63	.229
	4 Hours After	9.43 ± 1.78	9.68 ± 1.62	.585

Abbreviations: VM, volume minute per minute

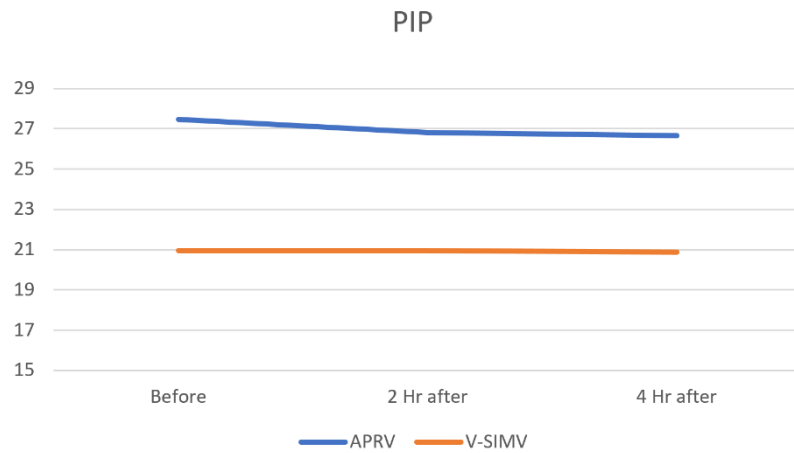


Figure 1. The mean of PIP in the stages of before up to 2 and 4 hours after intervention in the APRV and V-SIMV groups

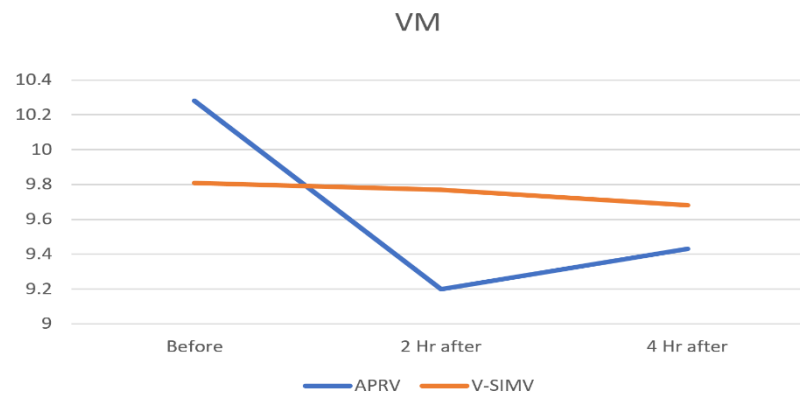


Figure 2. The mean of VM in the stages of before up to 2 and 4 hours after intervention in the APRV and V-SIMV groups

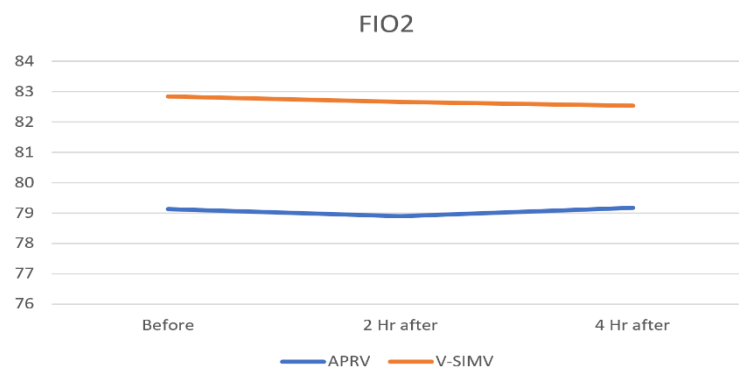


Figure 3. The mean of FIO2 in the stages of before up to 2 and 4 hours after intervention in the APRV and V-SIMV groups

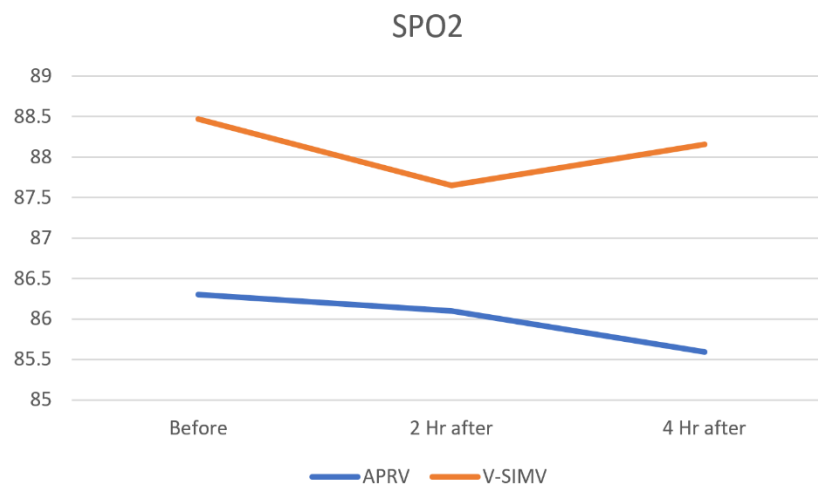


Figure 4. The mean of SPO2 in the stages of before up to 2 and 4 hours after intervention in the APRV and V-SIMV groups

Discussion

Managing ARDS patients, specifically those with COVID-19 has always been challenging. Notably, basic and common ventilation modes seem to fail to meet these patients' needs for proper ventilation; hence, alternative modes, including APRV, are recommended (19). The primary aim of this study was to demonstrate significant differences in the implementation of APRV mode compared to SIMV mode. APRV has been proposed as an alternative to SIMV. Because in APRV mode, the time spent on low positive expiratory end pressure (PEEP or P_{low}) is minimal and increases the mean airway pressure (P_{aw}) to the maximum possible by increasing the time spent at P_{high} (20, 21). According to the results of our study, the mean of PIP was significantly higher in the APRV group compared to the SIMV group. Swindin et al. argued that APRV uses longer inspiratory times, which increases mean airway pressures (8). Fredericks et al. also discussed that because of the inverse ratio of inspiratory to expiratory time, APRV generates higher mean airway pressures than conventional ventilation modes (10). Barotrauma is a complication of high airway pressure (22). Therefore, complications and increased mortality in patients undergoing

mechanical ventilation with APRV mode may be associated with the incidence of barotrauma and volutrauma-related complications such as pneumothorax, pneumomediastinum, and subcutaneous emphysema (8). However, in this study, there was no evidence of these complications in the subjects.

Our study showed that APRV mode could not effectively improve the VM and SPO2 of COVID-19 patients. Brower argued that APRV mod was associated with a reduction in mortality, not an increase in oxygenation and tidal volume (23). However, Mehaffey et al., and Sun et al., found that APRV could improve oxygenation in patients with hypoxemic respiratory failure (24, 25). Healthcare providers adjust APRV individually and with different applications. Therefore, due to the challenge of reproducing the APRV protocol in various studies, it isn't easy to compare the results of these studies (20, 26, 27).

As an unclear ongoing process, the treatment of COVID-19 should be based on clinical trials. Nonetheless, it is necessary to conduct further studies and clinical trials since the collected data are insufficient. Despite the effectiveness of the APRV mode in ARDS patients, the limited scientific evidence about the nature of COVID-19 makes it difficult to justify the reasons for the ineffectiveness of this mode in the ventilation of COVID-19

patients. With the increase of human knowledge about the nature of COVID-19 in the future, it will be possible to introduce new and effective methods for the ventilation of these patients.

This study has several limitations. 1. multiple organ failure or other comorbidities other than COVID-19 predisposed patients to a higher mortality rate. Therefore, the evaluation of this ventilator mode was not appropriate for these patients. 2. Patients' drug history and baseline hemodynamic indices were not assessed in this study. 3. Some confounding factors such as the severity of hypoxemia and Pao₂/Fio₂ ratio were not assessed in this study. These factors might have affected our findings.

Conclusion

In COVID-19 patients, the two mechanical ventilation modes of APRV and SIMV did not have significant differences in terms of FIO₂, VM, and SpO₂. However, the mean of PIP reduction in APRV mode was higher than in SIMV mode. Considering that several factors can affect SpO₂ and ventilation indices, these results should be considered with caution.

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